B1 Contd.

concentration level between about 35 pg/ml and about 80 pg/ml, whereby subsequently the administration of the LHRH antagonist is ceased.

II. REMARKS

Preliminary Remarks

This response is timely filed as it is accompanied by a petition for an extension of time to file in the third month and the requisite fee. This response is also accompanied by a notice of appeal, to preserve the applicants' rights.

Entry of the foregoing amendment (to claim 2) is requested pursuant to 37 C.F.R. §1.116 as the amendment will place the claims in better form for appeal (should the examiner maintain the rejections upon consideration of the following).

As a convenience to the examiner, actual amendment changes are set forth in the appendix, attached hereto.

Rejection Based Upon 35 U.S.C. §103(a)

The examiner rejected claims 1-13 and 28-31 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,663,145 (hereinafter Engel '145 in view of U.S. patent No. 5,658,884 (hereinafter Hodgen '884) and Nachtigall *et al.*

The examiner again asserted that Engel '145 teaches (1) a method of administering the LH-RH antagonist, Cetrorelix, in two phases, to a patient for treatment of endometrial hyperplasia, and (2) that the dosages of Cetrorelix useful in the method is 1 gm to 60 mg. The examiner then asserted (again) what the cited primary reference does **not** teach: (1) expressly teach the use of other agents in the method of treating endometrial hyperplasia; (2) expressly teach that the administration of the LH-RH antagonist causes the estrogen serum level to be 45-75 pg/ml or 50-75 pg/ml; (3) expressly teach the time and the frequency of

Cetrorelix administration; and (4) expressly teach the LH-RH antagonist to be administered on cycle day one to three.

The examiner then referenced the first secondary reference, Hodge '884, asserting that the issued U.S. patent teaches administration of an LH-RH antagonist in a method of treating endometriosis such that the estrogen level would be between 35-50 pg/ml. With respect to the second secondary reference. Nachtigall *et al.*, the examiner asserted that the cited document teaches Danazol (an isoxazol derivative of 17-alhpa-ethinyl testosterone, oral contraceptives, NSAIDS and other analgesics are useful in treating endometriosis.

In sum, the examiner asserted that it would have been obvious to employ Cetrorelix and other agents herein for a method to treat endometriosis. The examiner further stated that it is *prima facie* obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The applicants respectfully traverse the rejection and assert that the pending claims are not obvious over Engel '145 either alone or in combination with Hodgen '884 and/or Nachtigall *et al.* The applicants submit that Engel '145, either alone or in combination with Hodgen '884 and/or Nachtigall *et al.* fail to teach or suggest the applicants' presently claimed invention (*i.e.*, fails to teach or suggest all of the claim limitations) of a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term

induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist (claim 1) or the foregoing method wherein the LH-RH antagonist is administered in a dosage to achieve the estrogen serum concentration level between about 35 pg/ml and about 80 pg/ml (claim 2).

The primary reference, Engel'145, simply discloses a kit comprising an initial dose of an LH-RH antagonist suitable for treatment of hormone dependent conditions, and at least one maintenance dose of the LH-RH antagonist. The kit is suitable for a combination treatment regiment in which an initial dose is followed by several maintenance doses. In contrast, the claimed invention is directed to a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

As admitted to by the examiner, Engel '145 does **not** specify either the time period or frequency of administration or the amounts of the LH-RH antagonist to achieve the estrogen serum level of between 35 and 80 pg/ml nor does the cited document teach or suggest any follow-up treatment or therapy with progestine/gestagens or androgens for further prevention of ovulation besides menstrual and endometrial bleeding to avoid re-occurrence of symptoms or new endometric. Additionally, an immediate follow-up therapy with non-steroidal anti-rheumatic agents or analgesics is also not disclosed or suggested in Engel '145.

The first secondary reference, Hodgen '884 does nothing to cure the deficiencies of Engel '145. The examiner cited Hodgen '884 as teaching administration of the GnRH antagonist such that the estrogen level between 35 and 45 pg/ml is achieved. Hodgen '884 actually **does** disclose that a 24 hour serum estradiol level in the range of 35 to 45 pg/ml can

be achieved in monkeys by administering LH-RH antagonist. However, Hodgen does not give any dose range of the LH-RH antagonist. The dose has to be determined according to the results of an expensive and time consuming progesterone challenge test.

Furthermore, unlike the presently claimed invention (*i.e.*, short term induction), Hodgen '884 is directed to long-term treatment intervals, such as a number of years of therapy. See column 9, lines 3-6. The teachings of Hodgen '884 simply do not teach or suggest applicability of the long-term treatment study conducted on primates to a short-term induction treatment period. There is no teaching or suggestion from Hodgen '884 that an effective therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction may be achieved by a short 4-to 12 week induction treatment. Moreover, similarly to the Engel '145, Hodgen '884 does not disclose any follow-up therapy.

In view of the foregoing, it is submitted that Engel '145 and Hodgen '884, either alone or in combination, neither teach nor suggest a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LH-RH antagonist.

The examiner further cited Nachtigall *et al.* as teaching use of Danazol, an oral contraceptive, for treatment of endometriosis. Once again, nothing in this reference suggests the claimed method, involving administering to a patient of LH-RH antagonist for a short-term induction period. Furthermore, while Danazol is useful in treating endometriosis, due to the occurrence of severe side effects, it is common knowledge that treatment of endometriosis with Danazol has been largely abandoned nowadays.

Oral contraceptives do not cure endometriosis. As disclosed on page 766, column 1, last paragraph of Nachtigall *et al.*, "there are few data to support the use of this class of drugs. No controlled or comparative trials have been performed to confirm efficacy, making this treatment approach at least acceptable of the medical therapies available." The reference, therefore, teaches away from use of oral contraceptives in treatment of endometriosis.

Non-steroidal anti-rheumatic agents and analgesics are discussed for the treatment of pain as well as of inflammation. *e.g.,* of patients with chronic adhesions or with low grade stages of the disease. These agents are not effective in curing patients with severe or chronic endometriosis, not even in the short term.

The examiner further states that it is *prima facie* obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose. It is well known in the art of therapeutic treatment of patients, that combining pharmaceutical agents can not be done freely, even if they are known for the same purposes. Combination of pharmaceuticals often leads to serious side effects due to their potential interaction. Moreover, as discussed above, the invention is not directed to to a combinatorial treatment, but rather to a follow-up treatment, and, therefore, the reasons for combining agents given by the examiner are simply not applicable to the claimed invention.

Also, according to the examiner's statement, optimization of parameters, such as dosage range, dosage frequency, and timing is obvious as being within the skill of the artisan. While routine minor adjustments of dosage and its frequency may well be within the skill of an ordinary artisan, reduction of treatment time from years of therapy as taught by the references to a maximum of three month periods, as claimed in the instant invention, can hardly fall within the meaning of "optimization." In fact, modifying the treatment regiments disclosed in the cited references to shorten them to 4 to 12 week induction treatments would

render the treatment regimens disclosed in Engel '145 and Hodgen '884 unsatisfactory and non-useful for the intended therapeutic treatments.

It is, therefore, submitted that the references alone or in combination do not suggest the claimed therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LH-RH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment with subsequent termination of LH-RH antagonist administration.

With respect to the examiner's specific comments, the applicants submit the following remarks.

The examiner admitted that Engel '145, the primary reference, teaches a two phase treatment of endometrial hyperplasia, using a dosage of 1 mg to 60 mg. The examiner also admitted that Engel '145 fails to teach the claimed time and frequency of cetrorelix administration, the claimed serum estrogen levels, or the follow up treatment with contraceptives, NSAIDs, analgesics, and certain androgens, as claimed. By contrast the claimed treatment is a specified short term regiment, and is not limited to an initial high dose followed by maintenance doses. The present method requires a short term treatment during which serum estradiol levels are kept within the early follicular phase range of 35-80 pg/ml. In short, the examiner admitted that Engel '145 fails, at a minimum, to even suggest the claimed invention, and therefore is severely deficient as a reference for a rejection based upon 35 U.S.C. §103(a).

The examiner contended that a skilled artisan would combine the teachings of Hodgen '884 with Engel '145 to arrive at the claimed short-term therapy. The examiner stated that Hodgen '884 teaches treatment with an LH-RH antagonist for a period up to 97 days, which the examiner asserted is close to the claimed dosing frequency. Although the examiner cited no

support in the specification for this assertion, it appears to the applicants that the examiner is relying on the dosing data set forth in Table 1 of Hodgen '884.

The applicants submit that the examiner has incorrectly analyzed the experimental data, and has ignored the sentence immediately following Table 1 in column 8, lines 55-58, wherein the data are described as evidence of the "utility of titering individualized GnRH ant [*sic*] doses to amenorrhea, while maintaining tonic ovarian estradiol secretion in a milieu suitable for extended therapeutic regimens." The actual treatment regimen of Hodgen '844, as previously noted to the examiner, suggests that 6 months is too short, and that a regimen lasting years is desirable.

The claims are not directed to a method requiring pre-therapeutic regimen titering. In fact, the specification teaches that the claimed method does **not** require titering of the dosage of LH-RH antagonists. Thus, it appears that the examiner is employing faulty logic in attempting to maintain the position that Hodgen '884 teaches something "close" to a 4-12 week treatment regimen for endometriosis.

Finally, the examiner continues to assert that a skilled artisan would read Nachtigall *et al.* to mean that various NSAIDs and contraceptives are useful in treating endometriosis. While it is true that Nachtigall *et al.* teaches that oral contraceptives, GnRH analogs and testosterone derivatives are each separately useful in treating endometriosis, the cited document does not teach their combinations in treatment regimens (notwithstanding the fact that the present invention is directed, *inter alia*, to follow-up therapy) . To the contrary, Hodgen '884 only teaches that combining surgical and medical (pharmacological) treatments may be desirable in managing the condition. The actual teachings of Nachtigall *et al.* rebut the examiner's assertion that it is *prima facie* obvious to combine the disclosed agents. Perhaps the examiner thinks such combinations are obvious, but those skilled in the art (Nachtigall *et al.*) did not seem to agree with this premise in 1994.

Nachtigall *et al.* does not teach nor suggest the follow up therapy required by the claims, or that more than one medical treatment is desirable. Nachtigall *et al.* certainly does not supplement the deficiencies of the combined teachings of Engel '145 and Hodgen '884 with respect to the claimed short-term treatment regimen administering an LH-RH antagonist for a period of about 4 to 12 weeks.

In view of the foregoing, the applicants submit that the pending claims are not obvious over Engel '145 in view of Hodgen '884 and Nachtigall *et al.* and therefore request that the rejection based upon 35 U.S.C. §103(a) be withdrawn.

III. CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue that the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number indicated below.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____

Thomas A. Cawley, Jr., Ph.D.
Reg. No.: 40,944
Tel. No.: (703) 905-2144
Fax No.: (703) 905-2500

TAC\smm
1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000

Enclosure: Appendix

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 2 is amended as follows:

2. (Twice Amended) [A method according to claim 1] In the method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction, the improvement consisting of administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, wherein the LHRH antagonist is administered in a dosage to achieve the estrogen serum concentration level between about 35 pg/ml and about 80 pg/ml, whereby subsequently the administration of the LHRH antagonist is ceased.

End of Appendix